Best Pharmaceuticals for Children Act (BPCA)
Pediatric Formulation Initiative (PFI) Working Meeting
December 6–7, 2005
Bethesda, MD

Welcome and Introduction

Donald R. Mattison, M.D., National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS)

Dr. Mattison welcomed participants to the Pediatric Formulation Initiative (PFI) planning meeting and thanked them for their efforts during the many conference call meetings that led to this event. The stimulus for this initiative originated from the Best Pharmaceuticals for Children Act (BPCA), which specifically states that special attention needs to be focused on formulations for children. He hoped that this meeting would result in a set of directions to the NIH and perhaps other organizations and entities to help them more fully understand the issues. He then gave special thanks to Dr. Giacoia, who has worked hard on this initiative.

Meeting Objectives

George Giacoia, M.D., NICHD, NIH, DHHS

Dr. Giacoia explained that the purpose of the meeting was to explore a range of issues and challenges in creating pediatric formulations. The objectives of the meeting were to identify issues; stimulate discussions among meeting participants; and identify future PFI activities in which the government, industry, and academia can work together to ensure that pediatric formulations are created. He said that meeting participants would review ongoing activities, planning, and harmonization of the activities of the different groups and develop an overall plan for future activities.

He said that many barriers block access of children and infants to important drugs. During the last 10 years, a number of issues have been addressed:

- Analytical
- Pharmacokinetics/pharmacodynamics (PK/PD) approaches
- Scientific
- Logistical
- Legal
- Ethical
- Programmatic
- Regulatory.

Dr. Giacoia discussed pediatric labeling benchmarks and pediatric formulations:

- 2002 Best Pharmaceuticals for Children Act (consideration for list placement if reformulation of a drug is necessary)
- 2003 Pediatric Research Equity Act (PREA) (application shall contain data using appropriate formulations for each group).

He described a pediatric quagmire consisting of:

- Adult formulations
- Extemporaneous formulations
- Adequate formulations for age
- Home preparation
- Dispensing by parents.

He said that unanswered questions include the following:

- Are oral liquid preparations the gold standard for young infants and children?
- Can other fast dissolving oral formulations partially replace liquids?
- What is the role of alternative drug delivery systems?

Appropriate formulations for children of different ages have not been well defined or studied. The European Agency for the Evaluation of Medicinal Products (EMEA) formulations group developed an initial draft of a paper to attempt to address the problem. Dr. Giacoia listed dosage forms that could be used in pediatrics as alternatives to tablets and capsules:

- Oral granules
- Oral thin strips
- Oral effervescent granules
- Chewing gums
- Troches
- Oral fast disintegrating formats
- Freezer pops
- Lollipops
- Gummy gels
- Chewables
- Oral syringes.

Overall, it is imperative to identify the scope of the problem with pediatric formulations. This includes the total number and type of formulations needed, as well as the number and type of formulations by developmental age group. Dr. Giacoia said that considering the economic realities, it might facilitate finding solutions if the group kept in mind the needs for similar types of formulations in neurologically compromised and geriatric patient populations. National surveys on pediatric formulations can be found in:

- Pai V. Nahata. J Pediatr Pharmacol Ther 2001;6:107–119 (lists 113 drugs for which oral formulations are required)
- Lloyd Allen. USP Expert Committee on Pharmacy Compounding, 2001 (number of drugs for which oral formulations are needed in pediatrics: 71).

Looking at the list of pre-PREA and off-patent drugs, it is obvious that the cost of developing pediatric formulations will be very high. The economics working group estimated that it costs approximately $8–15 million per drug for chemistry, manufacturing, and control (CMC). This does not include the cost of clinical trials. Therefore, prioritization is necessary in order to decide which formulations should be developed first.

Dr. Giacoia pointed out that the global market for pediatric formulations is large:

European Union (2005)	100 million children
Projected (2015)	150 million children
United States (2005)	79 million children
Projected (2015)	100 million children

Approximately 17 of 71 drugs on the United States Pharmacopeia (USP) list requiring pediatric formulations are available in Europe; 28 of 108 are available in the United Kingdom, the European Union, and Australia. One factor to consider is the feasibility of importing these formulations to the United States.

When the PFI was first established, the working groups were created and formats and processes were developed. It was planned to hold the first workshop within a year. The role of the technical focus groups was to:

- Determine priorities
- Discuss major issues and develop items for discussion in the workshop
- Prepare individual recommendations and action items for discussion at the workshop
- Participate as experts and not as representatives of individual organizations.

So far, the working groups have held many telephone meetings:

- Scientific working group: 9
- Economics working group: 6
- Taste and flavor working group: 5
- New technologies working group: 1.

The groups have operated in isolation, but Dr. Giacoia said that the time has come to establish synergy among all of the working groups.

Issues not included in the initial phase of the PFI are:

- Patient-related issues
- Bioavailability studies
- PK/PD/safety issues
- Study design
- Compliance issues/patient acceptability
- Documentation of formulations used in pediatric clinical trials
- Global market issues.

The objectives of this meeting are to:

- Review activities since inception of groups
- Review each group's objectives
- Review specific areas for consideration
- Develop a short-term action plan
- Review and prioritize a list of proposed deliverables

- Identify long-term objectives
- Discuss global issues of pediatric formulations
- Consider interactions with the EMEA formulations group and other groups (for example, the World Health Organization).

Dr. Giacoia listed the following as possible meeting outcomes:
- Publication of proceedings from various groups
- Publication of review articles, approaches to study designs, analysis of data on the number of drugs lacking appropriate pediatric formulations, and type of formulations needed
- Development of a prioritization approach for drugs for which appropriate formulation is essential
- Estimation of cost to develop off-patent formulations
- Research initiatives that take into consideration expert opinions expressed at PFI scientific workshops
- Gathering of factual public information that can be used by policymakers, regulatory agencies, industry, and consumer groups interested in solving the problem of the lack of appropriate pediatric formulations
- Workshop convened by a federal advisory committee (for example, NICHD advisory council, BPCA pediatric committee) to develop recommendations to address the lack of adequate pediatric formulations
- Determination of unwarranted practices in dispensing adult formulations by pharmacists, health professionals, and consumers
- Development and implementation of education program on appropriate utilization of formulations in pediatrics
- Implementation with or by other organizations (United States Pharmacopeia, Pediatric Pharmacy Advocacy Group, EMEA, Agency for Healthcare Research and quality) of initiatives/projects developed as a result of PFI.

Dr. Giacoia believes that science, money, and commitment from all parties, including industry, academia, and government, are needed to resolve the problems with pediatric formulations. He closed his presentation by quoting Leonardo Da Vinci: "He who is fixed to a star does not change his mind."

EMEA Paediatric Drug Formulations and the PFI: Addressing a Global Issue

Tony Nunn, Ph.D., Department of Pharmacy, Alder Hey Children's Hospital and University of Liverpool, United Kingdom

Dr. Nunn thanked the NIH for inviting him to speak about pediatric formulation development in Europe. He said that the formulation initiative in the United Kingdom and Europe is primarily driven by pharmacists, not medical doctors. Dr. Nunn is the clinical director of pharmacy at a large children's hospital and is also the associate director of a clinical trials network that has recently been set up in the United Kingdom. He said that the European Union (EU) currently comprises:
- 25 countries
- 454 million people

- 100 million children
- 11 official languages (the working language is English).

Member countries of the EU are:

- Belgium
- Denmark
- Germany
- Greece
- Spain
- France
- Ireland
- Italy
- Luxembourg
- The Netherlands
- Austria
- Portugal
- Finland
- Sweden
- United Kingdom
- Czech Republic
- Estonia
- Cyprus
- Latvia
- Lithuania
- Hungary
- Malta
- Poland
- Slovenia
- Slovakia

Dr. Nunn described relevant institutions in the United Kingdom and the EU. The body that authorizes medicines in Europe is the Commission on Human Medicinal Products, and the chair of that commission is a pediatrician. They are advised by the European Medicines Agency, the equivalent to the U.S. Food and Drug Administration (FDA). Several other advisory bodies work with the commission, including a pediatric working party. An ad hoc formulation group, set up as part of that working party, produced the paper on formulations of choice in pediatric populations, which was distributed to PFI participants. Each of the member states of the EU has its own regulatory bodies. Within the United Kingdom, for example, the regulatory body is the Commission on Human Medicines (CHM). The Medicines and Healthcare Products Regulatory Agency (MHRA) is the UK equivalent of the FDA. An extemporaneous working party is part of the National Health Service, which is pharmacist oriented and has no direct allegiance to any of those institutions.

The United Kingdom and EU have been reviewing U.S. pediatric legislation to see if that will help introduce appropriate formulations from the United States into the United Kingdom. The EU is currently developing regulations that will be in place in 2007. In the meantime, the United Kingdom uses an interim strategy that allows importation of appropriate formulations authorized in countries with comparable regulatory systems. Work on the UK extemporaneous formulary includes identifying and prioritizing products of interest. The National Health Service and the Medicines for Children Research Network are researching extemporaneous formulations to improve quality. The British Pharmacopoeia (BP) is involved in evaluating formulation quality and adopting reviewed formulations into the BP to provide them with a legal basis. They have also been trying to engage the pharmaceutical industry about pediatric formulations and planning for the future.

Dr. Nunn analyzed licensing of medicines for children in the United States and found that as of June 2004, the following had occurred:

- 286 FDA "written requests"
- 346 proposals from industry
- 108 completed studies
- 98 exclusivity granted
- 74 new pediatric labels
  - Midazolam
  - Ranitidine
  - Enalapril
  - Gabapentin.

Ninety of the pediatric products worked on in the United States are available in the United Kingdom, but the majority of the data that had been submitted in the United States were not submitted to MHRA. The UK interim strategy is to:

- Obtain data from completed U.S. studies
- Work with British National Formulary for Children (BNF-C)
- Work with extemporaneous formulary
- Support EU legislation
- Conduct pediatric research
  - UK requirements
  - EU developments.

Dr. Nunn described the 20 top extemporaneous products in the United Kingdom.

Product	**Form**	**Comment**
Acetazolamide	Suspension	Suggested strength 50 mg/ml.
Allopurinol	Suspension	Suggested strengths 20 mg/ml; 60 mg/ml. Rosemont has 20 mg/ml as special.
Amiodarone	Suspension	Now authorized in UK for children but only tablets available. Suggested strength 10 or 20 mg/ml.
Captopril	Suspension	Authorized in Australia. Can be imported.
Clonazepam	Suspension	Authorized in Germany as drops.
Clozapine	Suspension	
Dexamethasone	Suspension	400 mcg/ml authorized from Rosemont. Other strengths unauthorized but available from Rosemont. Suggested additional strength 1 mg/ml.
Didanosine	Suspension	Suggested strength 10 mg/ml.
Ethambutol	Suspension	Suggested strength 100 mg/ml.
Gliciazide	Suspension	
Glycopyrrolate	Mixture	Suggested strength 200 mcg/ml and 5 mg/ml.
Hydrocortisone	Suspension	Suggested strength 1 or 2 mg/ml.
Lorazepam	Suspension	Suggested strength 500 mcg /ml.
Metoprolol	Suspension	Suggested strength 10 mg/ml.

Midazolam	Syrup	Authorized in United States but little used due to cost. Suggested strength 1 or 2.5 mg/ml.
Omeprazole	Suspension	Bioavailability may be only 50% if prepared with NaOH. Need a PPI liquid medicine which will go down small bore nasogastric tubes. Suggested strength 2 mg/ml.
Phenobarbitone	Elixir	Alcohol free product required; sodium salt acceptable. Suggested strength 10 mg/ml.
Pyridoxine	Suspension	Suggested strength 10 or 50 mg/ml.
Thyroxine	Suspension	Authorized in France as drops (5 mcg/drop). Can be imported. Anecdotal evidence of bioavailability problems with extemporaneous formulations. 25 mcg/ml.
Tranexamic Acid	Mouthwash	Suggested strength 50 mg/ml.
Vancomycin	Suspension	Suggested strength 25 or 50 mg/ml.

The UK Clinical Research Network, similar to the U.S. Pediatric Pharmacology Research Network, recently received 100 million pounds to set up five new research networks:

- Medicines for children
- Dementias
- Stroke
- Diabetes
- Mental health.

The medicines for children network, based in Liverpool, has £20 million to set up 8 or 9 local research centers in the next 5 years primarily to conduct phase 3 trials. The network will incorporate the following clinical studies groups:

- Allergy, infection, and immunity
- Anesthesia and intensive care
- Gastroenterology, hepatology, and nutrition
- Methodology
- Neonates
- Neurology
- Pediatrics, general
- Pharmacy and pharmacology
  - Formulation
  - Pharmacokinetics
  - Pharmacogenomics
  - Pharmacovigilance
- Respiratory and cystic fibrosis
- Others.

Dr. Nunn expects a work stream of formulations for children to go through that network. Europeans have been trying to build on what has been done in the United States on developing

pediatric formulations. Legislation called "Better Medicines for Children" is currently going through the European Parliament:

- Consultation document (April 2002)
- Draft regulation (March 2004)
- First reading European Parliament (September 2005)
- Operational from early 2007.

Key measures for new off-patent medicines/indications specifically developed for children include a new type of marketing authorization, the Paediatric Use Marketing Authorisation (PUMA), which:

- Enables 10 years' data protection
- Allows use of existing brand name (brand recognition)
- Amends data requirements.

PUMA also includes a requirement that if a company wishes to authorize a new medicine in Europe, it must submit a pediatric plan.

Another European initiative is a study fund called Medicines Investigation for the Children of Europe (MICE) which allows study of older drugs for which industry has little interest (for example, oral morphine for neonates). It is for use where other incentives are not available and is available to industry and noncommercial organizations. An expert advisory committee determines priorities and seeks studies.

A paper called "Formulations of Choice for the Pediatric Populations," which lays out the state of knowledge of pediatric formulations and how to proceed in developing them, was distributed to PFI participants. It was created by a European working group that included formulations scientists from industry, academia, and regulatory agencies. An accompanying letter said that its purpose was not to instruct industry, but rather to identify difficulties and consider ways to provide better formulations for children. Dr. Nunn added that the consultation period ends in December 2005. The document contains a table on preferred dosage forms for the pediatric population based on developmental age.

	Preterm	Term	Infants and Toddlers	Child Preschool	Child School	12–18
Drops	++	++++	+++++	+++++	+++	++
Liquid	++	++	+++++	+++++	+++	++
Multi-particulate	+	++	++	++++	++++	+++++
Tablet	-	-	+	+++	++++	+++++
Chew tablet	-	-	+	+++	+++++	+++++

"Melt" tablet	-	+	++++	++++	+++++	+++++

Drs. Nunn and Giacoia compared the lists developed in 2001 of extemporaneous formulations, and the results are contained in the following table.

	United Kingdom	United States	
Preparations in list	42	108	
Authorized/labeled in UK, EU, Australia		28	26%
Common to both lists	24	24	22%
UK also interested		43	40%
Subtotal		95	88%
UK not currently interested		17	16%

Dr. Nunn pointed out that 28 of the medicines currently prepared extemporaneously in the United States are authorized and labeled for use in the United Kingdom, Europe, and Australia. For example, trimethoprim is prepared on the bench in the United States, but has been authorized in the United Kingdom as a liquid preparation for more than 20 years. He wonders why the United States does not import this product, given the risks of compounding and the number of documented deaths from inappropriately prepared extemporaneous formulations.

Dr. Nunn presented a continuum of risk management issues. The highest risk is from extemporaneous compounding, followed by products produced by "specials" manufacturers that are licensed and regulated in the United Kingdom to manufacture medicines to good manufacturing practice (GMP). This provides quality assurance, but not safety or efficacy. Less risky are licensed imports; while the safest products are licensed and labelled products. Dr. Nunn stated that the United Kingdom and European countries have regulated importation of appropriate, authorized pediatric formulations from other countries with similar regulatory oversight, but the United States imports virtually nothing.

Dr. Nunn referred participants to the following article: Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Brion F, Nunn A, Rieutord A. Acta Paediatr 2003; 92: 486-490.

Questions and Comments. A participant asked to what extent pediatric formulations are imported into the United Kingdom. Dr. Nunn replied that there are extensive importations. He said if he is asked to provide a medicine that is not an authorized medicine in the United Kingdom, his first step is to check if it is licensed in Europe, the United States, or Australia. He would not check with India or South America because of quality issues in those areas. Medicines are normally imported to the formulary at individual hospitals. He added that the Department of Health includes an agency that reviews discontinued medicines, which is a significant problem in

pediatrics because many medicines are discontinued when they are no longer commercially viable.

Extemporaneous Formulations: Comparison with Labeled Pediatric Formulations

Karen Thompson, Ph.D., Research Labs, Merck and Company, Inc.

Dr. Thompson said she was honored to speak on behalf of the extemporaneous subgroup, which has been meeting by teleconference call. She is a formulator with 18 years of experience and has developed both extemporaneous formulations and final products for pediatric populations.

Extemporaneous formulations have many unique properties, but there is some overlap between extemporaneous formulations and general formulation development. Work group discussions have centered on scientific and development issues of pediatric formulations. Dr. Thompson said that the issues surrounding extemporaneous formulations have not changed since the FDA 1998 workshop on formulations, and she looks forward to developing an action plan to overcome these problems. Goals for this meeting include:

- Develop and prioritize a list of issues
  - Extemporaneous formulations
  - Pediatric formulations
- Discuss and focus scientific issues
- Develop action plans
  - Short-term goals
  - Long-term goals.

Extemporaneous formulations are prepared at pharmacies or hospitals for patients, and some of the compounding vehicles and diluents have limited or no availability overseas. Some diluents and vehicles also can change somewhat in composition over time of manufacture, and notification is necessary to assess the impact of the change on the formulation.

The largest liability with extemporaneous formulations is quality control:

- Site to site
- Degree of product handling/manipulation.

Quality control requires that established recipes are being followed and that the patient is receiving the proper dosing.

Another issue is formulation compatibility with dosing technologies, such as droppers, syringes, and packaging. If a parent uses a kitchen teaspoon instead of a dosing syringe, the variability in volume can be quite extreme. Some formulations adhere to various surfaces and that information needs to be given to parents to ensure that the child is given the proper dose.

According to Dr. Thompson, the group spent considerable time discussing how to develop and use a reporting database. They discussed how to obtain data from HMOs and hospitals and provide it to this initiative or the industry to help pediatric populations. Another issue is how to fund development efforts for off-patent medications.

General pediatric formulations development problems that are not specific to extemporaneous formulations include:

- Analytical monitoring
  - Stability (tested to International Conference of Harmonization [ICH] conditions)
  - Microbial (the more handling, the more risk; acceptability of preservatives in younger populations)
  - Validated methodology
  - Suspendability (dose uniformity)
- Organoleptic properties
  - Taste/smell (taste preferences shift with age; cultural preferences)
  - Texture (for example, will a gritty suspension be acceptable to young children?)
- Population considerations
  - Dosing volume
  - Formulation age-appropriateness
- Biopharmaceutics
  - PK/PD
  - Applicability of Biopharmaceutical Classification System (BCS) classification.

The BCS classification system is used to monitor risk of using formulations in patient populations. For instance, in a highly permeable, highly soluble Class 1 preparation, the PK risk is relatively low. If one uses a low solubility, high permeability class 2 preparation, sometimes there is inadequate volume to allow the medication to dissolve. Permeability change in infants versus adult formulations is problematic. The highest risk occurs with class 3 compounds because they have poor permeability and poor solubility. If one uses the standard adult solubility in 250 mls, does that apply to a neonate whose stomach volume is far lower than 250 mls? Should modification occur to extend to pediatric patients? The group also discussed utilization of data to obtain waivers.

Short-term strategies include:

- Utilize this meeting to provide focus and deliverables for the extemporaneous team
- Develop tools to access the acceptability of extemporaneous formulations worldwide
  - Roadblocks
  - Opportunities.

Mid-term strategies include:

- Possible data collection opportunities
  - Examine pharmacy survey data and discuss focus
  - Develop template for accessing data in HMOs
  - Collect data from vehicle manufacturers and extend availability to worldwide centers
- Establish centers of excellence
  - Conduct pediatric studies (for off-patent medications as needed)
  - Disseminate information
  - Monitor clinical use (efficacy, safety)
  - Logistical concerns including funding and intellectual property issues.

In summary, Dr. Thompson said the group has developed a list of items based on concerns about pediatric formulation development and extemporaneous formulation development. They have also developed some ideas for collecting data in the field. She closed by saying the meeting today provides a face-to-face forum to develop action plans and will provide tremendous value to the scientific community and children worldwide.

Regulatory Challenges

Samuel D. Maldonado, M.D., M.P.H., Johnson & Johnson; Chair, PhRMA Pediatric Task Force

Dr. Maldonado related an experience that occurred when he was a medical officer at the FDA in the division of antiviral products. The commissioner of the FDA had called to ask him about the problems with protease inhibitors formulations for children. He was able to reassure the commissioner that the problem was scientific, not regulatory. Dr. Maldonado explained that he knew of one company that had tried to develop 200 different formulations for a single pediatric drug, and each attempt failed.

He explained that formulations used for children are also sometimes used for geriatric patients and other adults if the volumes permit. He then gave a brief overview of some tragedies that had occurred with pediatric formulations, including:

- Sulfanilamide elixir in diethylene glycol (1938) caused the death of many children
- Benzyl alcohol in neonates caused metabolic acidosis and death
- High content of sodium or potassium in parenteral formulations caused electrolyte imbalances.

Good formulations for pediatric use are difficult to develop, but they are the key to accurate, safe, and compliant therapy. Points to consider are:

- The pediatric population is heterogeneous and several formulations may be needed.
- Appropriate formulations are needed for adequate clinical trials.
- A good formulation is key for compliance.
- Pediatric formulations may be used by geriatric patients and other adults who cannot swallow solid formulations.
- Liquid formulations may allow for more accurate dosing by body weight or body surface area.
- Palatability is paramount (except for suppositories).

Dr. Maldonado explained some of the popular categories of formulations used in children:

- Liquid oral formulations
  - Solutions
  - Suspensions
  - Elixirs
  - Syrups
  - Drops
- Solid oral formulations
  - Chewable tablets

  - Smaller tablets/capsules/caplets
- Other formulations
  - Transdermal
  - Suppositories.

Because acetaminophen is a very bitter substance, the manufacturers of Tylenol have created many different classes of drug products to deliver this medication, including:

- Infants' Tylenol
- Children's Tylenol
- Jr. Tylenol
- Infants' Tylenol Cold
- Infants' Tylenol Cold Plus Cough
- Children's Tylenol Cold Daytime
- Children's Tylenol Cold Plus Cough
- Children's Tylenol Cold Nighttime
- Children's Tylenol Cold and Allergy
- Children's Tylenol Flu
- Simply Cough
- Simply Stuffy
- Children's Tylenol Dye Free (cherry flavor)
- Children's Tylenol meltaways
  - Wacky watermelon
  - Bubblegum burst
  - Grape punch
- Children's Tylenol suspension liquid
  - Cherry blast
  - Grape splash
  - Bubblegum yum
  - Very berry strawberry.

Dr. Maldonado stressed that from a regulatory perspective, each of the different formulations he listed is a separate drug product that requires approval by the FDA. Each of the Tylenol products listed above has a dedicated line production. Dr. Maldonado then related a story about the composition of baby food for different cultures showing how flavor and palatability are important aspects of pediatric formulations.

Dr. Maldonado explained that drug sponsors have to maintain each drug product by:

- Complying with the regulatory requirements of each drug product individually
- Maintaining an open line production for each drug product (complying with GMPs for each product)
- Ensuring the safety profile of each drug product individually and comparing to other products with the same drug substance.

Some of the challenges he outlined were:

- There are pediatric formulations that have more product in stability shelves than what they sell in the marketplace.
- Some pediatric formulations that work well in clinical trials cannot be scaled up with the same physicochemical profile.
- Liquid formulations typically have shorter stability times than solid formulations, making it necessary to replace drug product more often.

The charge of the FDA's pediatric formulations working group is to lessen the CMC barriers to new formulation development. The working group:
- Was formed in December 1995
- Includes representatives from Pedicomm and from the Office of New Drug Chemistry.

An FDA workshop, held on May 11–13, 1998, concluded that CMC and regulations appear not to be major barriers for new formulations.

Dr. Maldonado said that water and alcohol were the primary solvents used in formulations, but alcohol is not suitable for certain pediatric subpopulations. He believes that much work can be done on solvents, especially for oral or liquid formulations. More research needs to be done on excipients, including:
- Additives
- Colorants and flavors
- Tolerance and safety.

The pediatric advisory subcommittee met in April 2001 and recommended that formulations appropriate for pediatric use should be developed to ensure safety and consistency in administration. These formulations must be palatable and permit easy dose titration. In some cases, it would be desirable to have more than one formulation available (for example, suspensions, chewable tablets, sustained release, and transdermal).

Dr. Maldonado explained that the FDA continues encouraging sponsors to develop appropriate pediatric formulations and has shown flexibility and understanding when sponsors run into technical and scientific difficulties in the development of formulations. In these cases, the sponsor and the FDA look for alternatives in providing appropriate information on dosing and dosage forms for pediatric patients. He emphasized that there are not regulatory barriers in place, but several scientific challenges to overcome.

Tasks for the future are:
- Continue looking for opportunities to ease regulatory requirements that may lead to the creation of more pediatric formulations
- Research alternative solvents
- Research alternative routes of delivery
- When the creation of a new pediatric formulation is impractical, look for alternative ways to inform on dosing.

Testing for Taste and Flavor in Children

Julie A. Mennella, Ph.D., Developmental Psychobiologist, Monell Chemical Senses Center

Taste and smell are human's oldest senses. These senses are vigilant gatekeepers that evolved to reject what is harmful and encourage eating what is beneficial. Dr. Mennella said that the objective of the taste and flavor working group is to summarize the current knowledge of:

- Sensory development
- Drug palatability
- Taste masking and bitterness reduction
- The appropriateness of current pediatric taste tests.

Another goal of the group is to identify gaps in knowledge. Dr. Mennella hopes this information will help participants understand the sensory world of the child and help lead to new technologies that enhance drug acceptance and compliance in pediatric populations.

Dr. Mennella said that children and adults are subject to many of the same ailments and diseases, and by necessity, are often are treated with the same drugs. However, common methods of blocking bitter tastes with encapsulation can be ineffective for young children because they often cannot or will not swallow pills or tablets. Noncompliance due to taste issues is one of the leading reasons for therapy failures. Dr. Mennella posed the question: Does taste also contribute to the complicating factor of medication noncompliance among parents?

Chemical senses are a fusion of taste, smell, and chemesthesis/irritation. Tastes can be broken down into five primary tastes: sweet, sour, salty, bitter, and umami. Humans perceive many different odors, perhaps thousands. Odors are perceived when they bind to the olfactory receptor in the nose and when substances in the mouth reach the retronasal receptors. Chemesthesis/irritation includes pain, cooling, tingling, stinging, burning, and variation in temperature. When foods or liquids are in the mouth or throat, the perceptions arising from all of these senses combine to determine flavor.

To illustrate that taste is a fusion of these senses, Dr. Mennella encouraged participants to hold their noses and put two jelly beans in their mouths. Most of what they experienced was taste, primarily sweetness. However, when the nose was unplugged, the odor allowed them to differentiate between the watermelon and strawberry flavors. She pointed out that many cross cultural taste preferences are primarily odor based.

There are a small number of taste qualities**,** which from an evolutionary perspective serve important biological functions:

- Sour—acids: Ripeness?
- Salty—NaCl, LiCl: Sodium, minerals?
- Bitter—alkaloids, peptides, toxins: Poison avoidance?
- Umami—glutamate, aspartate, nucleotides: Protein? Calories?
- Sweet—sugars, high intensity sweeteners: Calories for plant-eating animals.

In nature, bitterness is often associated with toxicity. Bitterness is an innately aversive sensation in human newborns, adults, and other animals. In contrast, sweetness, an innately pleasant sensation, is associated with readily available calories from carbohydrates. Children around the world can discriminate different sugars and will show strong preferences for them within hours of birth. Sugar and salt are drivers of food and medicine acceptance in children.

Dr. Mennella explained that the oral cavity is an *in situ* pharmacological preparation:
- Sensory attributes may predict physiological attributes.
- The potency of a drug may be reflected in its sensory attributes.
- The more bitter a compound, the more effective it will be as a drug.
- The more bitter the compound, the greater the compliance problems with children.

One of the group's objectives was to summarize research findings to date on sensory development in children. One of the first questions considered was: When does ability to perceive tastes and flavors begin?

Taste development *in utero*:
- Taste buds are present by the second month.
- Taste pores are present by the fourth month.
- Evidence suggests that the fetus can respond to sweet and bitter tastes and flavors *in utero*.
- The sensory world of children is different from that of adults: Heightened preference for sweets and salt and rejection of some bitter tastes are present during development.

Dr. Mennella said that adult taste panels are not able to predict tastes that children prefer and those they will reject because of these differences in taste perceptions.

Olfactory development *in utero*:
- Primary olfactory receptors are present by the eighth week of gestation.
- Olfactory marker protein (OMP), a biochemical correlate of olfactory receptor function, is present by the sixth month of gestation.
- Olfactory memories can be formed *in utero.*

Odors of foods mothers consume are transmitted to the fetus through amniotic fluid and to newborns through breast milk. Therefore, taste biases are developed before and after birth. Because of this, developing a universal flavor for medications may be problematic.

Chemesthesis development *in utero*:
- The ethmoid and nasopalantine branches of the trigeminal nerve are differentiated and respond to tactile stimulation by about the tenth gestational week.
- Viscosity and irritation may play an important role in the acceptance of oral medications. However, there is very little research in this area.

Dr. Mennella stressed the paucity of data on the effect of viscosity and irritation in children's taste, and these senses can have a huge impact on acceptance of medications by children.

The group then explored basic research done on taste testing in infants and children. Contemporary research on the ontogeny of taste and smell is based on more than a century-long legacy examining behavioral responsiveness and determining functional maturity. Psychophysical studies provide information relevant to two aspects of chemical sensation: the sensitivity of the system to chemical stimuli and the hedonic valence of the sensation. Distinguishing sensitivity from hedonic responses is difficult to do in infants and young children.

The most widely used reflex-like responses used to evaluate taste in nonverbal infants include:
- Salivation
- Lateral tongue reflex
- Sucking measures
- Heart rate
- Facial expressions.

Dr. Mennella showed slides that clearly portrayed facial responses to sweet and bitter tastes in infants, demonstrating that innate stereotypical facial responses can be used in basic research. As children become more social with age, facial responses are less reliable.

The most widely used consummatory responses include:
- Multiple-bottle preference test (single test day)
- One-bottle tests (multiple test days).

Evaluation of facial expressions and reactivity include an anatomically based coding system (FACS) that specifies facial movements in terms of minimally distinguishable actions of facial muscles. This can be used to determine the frequency of a variety of positive and negative (for example, gaping) facial responses after placement of solution in the oral cavity of the baby. FACS data are less reliable in older children.

Convergence of responses from these different research methods show that:
- Infants and children like sweets.
- Infants and children can distinguish among different sweet tastes.
- Infants and children will reject bitter tastes.

Dr. Mennella explained that although each measure has its limitations, the convergence of findings from different methodologies will give confidence to conclusions.

Research done on taste testing in children was reviewed by the working group. Children differ from adults in perceptual sensitivity, cognitive maturity, emotional maturity, and physical maturity. When asked a question, many children answer in the affirmative. There are limitations to testing young children, and measures of re-test reliability and the subjects' understanding of the task should be included in every study. Suggestions for taste research in children include:
- Limit dependence on verbalizations.
- Avoid "what if" questions.
- Do not use "yes/no" questions.

In older children, the paired comparison method can be used to assess pairs of samples that differ in taste of flavor quality. More complicated tasks can be used in older children. Paired-comparisons, scaling tests, forced choice tracking procedures, and rank-order tests are the most widely used methods to measure hedonic responses to tastes, odors, and flavors.

In rank-order method, a sample is removed from the set after being selected, or a bifurcated approach is used in which the subject is first asked to place the sample into either a "good/like" or the "bad/dislike" category. The degrees of like or dislike are then scaled.

A hedonic rating scale is a frequently used method in pediatric studies. Little is known about its reliability and at what age children use the entire scale and not just the anchors. Some marketing research firms and researchers claim success with 7–9 point face scales with 5 to 7 year olds. Dr. Mennella said that it is important for the group to identify what is known and not known about taste research in children, including attention to whether research has been published in peer-reviewed journals.

Some of the gaps in knowledge identified by the group concerning taste testing are:

- Identify the types of questions that industry wants to ask children. The types of methods used depend on the question asked.
- More research is needed to determine reliability of methods that measure sensitivity and preferences in children. What is the best predictor for initial acceptance and chronic use acceptance?
- More research is needed on texture (for example, viscosity) perception, as it relates to oral medication.
- What questions can not be answered by adult panelists? When should children be used to assess the palatability and acceptance of oral medications and how might that facilitate short- and long-term compliance?
- How does medication usage and disease state (for example, fever, radiation, infectious agents) modify taste and smell perception?
- What is the evidence for a "strong association" for color and flavor? Does it impact acceptance of products?
- Identify questions that can be incorporated into clinical trials to systematically evaluate the taste issues as well as parental perceptions and biases. Full formulation information in all pediatric trial reports should also be included to improve validity and reliability of findings (Standing et al., 2005).
- Are there similarities with oral pharmaceutical acceptance in the elderly?

Dr. Mennella began her discussion of cultural taste preferences by noting that during infancy and childhood, children learn the rules of cuisine and the context in which flavors are experienced. The first experience with flavors occurs in amniotic fluid and mothers' milk because flavors of foods and beverages are transmitted to these fluids. Learning what flavors are associated with what foods and medicines begins in childhood. For instance, lemon is a commonly used flavor in England and chamomile is common herbal infusion in Mexico. However, bubble gum and cherry flavors are more common in the United States. Scientific evidence of flavor programming during infancy does exist. In one study, infants that consumed hydrolysate formulas by the third month

of life continued to accept these unpalatable hydrolysates at 7.5 months of age (Pediatrics, 2004). Experience with different flavors before sensitivity to flavors develops results in enhanced acceptance.

Gaps in knowledge about cultural taste preferences include:
- Does early and chronic exposure to drugs modify later acceptance in infants?
- Peer-reviewed studies on cross-cultural flavor preferences, bitter taste sensitivity, and other behaviors (for example, are U.S. children more finicky?) are needed.
- Individuals and cultural groups differ in their sensitivity and preference for bitter tastes and other flavors. To the extent these differences are genetic, studies of single nucleotide polymorphisms (SNPs) could classify people.
- What is modified by experience that leads to cultural preferences for flavors and retronasal odors?

Dr. Mennella next discussed blocking and masking bitter tastes. Bitter taste of pharmaceuticals is an ongoing formulation problem because of the diverse number of receptors and multiple transduction pathways and because the transduction mechanisms underlying bitter taste perception are not fully understood. A large family of taste receptor genes devoted to the detection of bitter tastes, the TAS2R genes, has been identified. Analyses of the human genome revealed that the hT2R family is composed of about 25 receptors. Each one could recognize multiple compounds, some of which are chemically related but some of which are not.

Research has focused on two approaches to managing bitter flavors:
- Bitter blocking (pharmacological antagonism of bitter compound activation or transduction pathways)
- Bitter masking (psychological interference with bitterness perception).

Dr. Mennella said that sodium is the most effective cation at inhibiting bitterness of oral pharmaceuticals (for example, Ranitidine, acetaminophen, pseudoephedrine) in adults. However, mechanisms underlying its effectiveness are unknown.

Studies on bitter taste in children that could help make oral pharmaceuticals more palatable to children are:
- Sodium suppressed the bitter taste of urea and caffeine in children.
- Salts may be effective bitter suppressors for some bitters (not all) since salty tastes are preferred by children.
- Use of electronic tongues and noses for initial screening of foods and beverages (for example, wine) is still in its infancy. Most of the applications of these technologies represent limited feasibility studies with poor reproducibility and predictive value. Sensor drift is a problem (Deisingh et al., 2004) and the technologies are not based on biological principles. Moreover, bitter taste perception is highly variable in humans. More research is needed to validate these methods and to determine predictive value for oral pharmaceuticals.
- Other technologies to explore are bitter encapsulation and sprinkles.

Regarding gaps in knowledge about bitter tastes, Dr. Mennella noted:

- Genomic-based receptor assay systems hold significant promise for discovery of novel flavor molecules and taste blockers. Identification of T2R receptor ligand pairs may lead to identification of mediators of bitter tastes.
- Genomics and other new cellular and molecular techniques will provide the tools for major advances in understanding of the biology of sensory systems. Practical discoveries will follow closely. For example, this may lead to development of blockers for all or most of bitter transduction at one or more common elements of the pathways.
- Bitter and irritation perception (for example, ibuprofen) in other parts of the oral cavity (throat). A major component of the throat irritation produced occurs via pH-dependent receptor mechanisms. Thus, ibuprofen and other drugs may stimulate a novel, pH-sensitive irritant system. This has implications for psychophysical testing as well. "Sip and spit" tests will not evaluate this type of perception.

In closing, Dr. Mennella said that she hopes learning which research methodologies are most appropriate for what ages and what questions industry would like to ask will allow determination of the effectiveness of these technologies.

Economic Issues

Emmett Clemente, Ph.D., Manchester Consulting Incorporated (via conference call)

Dr. Clemente said that he was happy to participate in the pediatric formulation initiative. He described his 35 years of experience in the pharmaceutical industry, 20 years of which were in large pharmaceutical companies. During that period he developed products for both adult and pediatric patients. He developed formulations for children from off-patent drugs, including liquid, capsule, and controlled release forms of theophylline, a bronchodilator. He was also involved in the development of the first liquid steroid for children. In 1989, he founded a small company, Ascent Pediatrics, dedicated to the needs of pediatrics. Between 1981 and 2001, his company developed and marketed Primisol, an antibiotic for middle ear infections in children, and Orapred, a steroid that included a taste masking technology.

The economics group was asked to consider the economic issues related to development of pediatric drugs and to estimate the chemistry, manufacturing, and control (CMC) elements of developing pediatric medications from off-patent drugs. The topics for Dr. Clemente's presentation include:
- The pediatric patient
- Important therapeutic categories in pediatric medicine
- Pediatric and adult markets
- Incentives.

Dr. Clemente discussed the pediatric marketplace, which he considers to be quite substantial. For example, he said the pediatric market for acetaminophen was approximately $300 million. However, if a company wished to develop a liquid formulation of acetaminophen for young children, the market shrinks to about $20 to $25 million. In developing pediatric products from off-patent drugs, a company must:
- Determine market size

- Estimate cost of development (CMC, clinical, regulatory pathway)
- Protect product (competition, patented technology, trade secret)
- Consider product line extensions (new dosage forms or those with new technologies).

Dr. Clemente said that it is very challenging to develop an off-patent drug because of the competition from large pharmaceutical companies that are developing new products. The economics group estimated that the cost for CMC only to develop an off-patent drug for pediatrics would cost between $8 and $15 million. Considering the regulatory pathway is important because the FDA division reviewing the submission determines the time it takes to develop and obtain approval for a product. Competition in the marketplace is keen, he said, and developing advances with off-patent drugs is a challenge. Many companies try to get a use and a formulation patent to protect the product. This can prove to be an impediment because after spending large amounts of money, the company may face generic competition in a short amount of time.

In discussing the pediatric patient, Dr. Clemente noted the following:
- Birth rate (4 million per year—2010)*
- Age considerations (newborn–16 years)
- Appropriate dose form (liquids, tablets)
- Special considerations: (taste, metered dose inhalers, nasal).

*U.S. Bureau of Statistics

Up to the age of 6 years, 60 percent of the dose forms used are liquids, 6 percent solids, and 19 percent injections. At 16 years old, liquid forms drop to 44 percent and solid dosage forms increase to 25 percent. Dr. Clemente pointed out that liquid forms are predominant in pediatrics, and creating liquid dose forms is challenging.

Important therapeutic categories in pediatrics are (estimated 2004 values, IMS Health Data):
- Anti-infective $3.852B
- Respiratory $1.529B
- Endocrine $1.021B
- CNS $0.894B
- Vaccines $1.196B.

Market size in billions:
- Pediatric* $10
- Adult And Pediatric** $189.

*Estimated 2004 Values, IMS Health Data
**Reed Business Information, 2002

When Dr. Clemente increased the adult and pediatric market 5 percent per annum to match the 2004 figure for pediatrics, he estimated that only 5.3 percent of the total current pharmaceutical market is pediatrics. He considers this the single most important factor that prevents large companies from developing pediatric products. Small companies and the government need to find ways to make drug development feasible for pediatrics. Possible incentives for industry are:

- Market exclusivity
- Combination of market exclusivity and reimbursement
- Tax considerations.

Dr. Clemente believes it will require substantial incentives to entice companies to develop off-patent products for pediatric use.

New Technology and Drug Delivery Systems

H. William Kelly, Pharm.D., Professor Emeritus of Pediatrics, Department of Pediatrics, University of New Mexico

Dr. Kelly explained that the new technology and drug delivery systems work group was recently formed and has had two discussions so far. He said that his area of expertise is in aerosol delivery and this talk would focus on that technology because oral delivery systems have been covered by other speakers.

He began by briefly mentioning dosage forms that can be used in the pediatric patient population:
- Oral
- Aerosol
- Injectables
- Topical (creams, adhesives)
- Suppositories.

Oral dosage forms currently available for children include:
- Chewables
- Liquids (flavored solutions or suspensions)
- Oral fast disintegrating formats (effervescent dosage forms)
- Gummy gels
- Pediatric dosing bottle
- Lollipops
- Freezer pops
- Troches (lozenges that dissolve in the mouth)
- Oral syringes
- Capsules (best for gradual release formulations)
- Oral granules (can be sprinkled onto foods such as applesauce)
- Oral thin strips (rectangular strips that dissolve quickly)
- Oral effervescent granules (add to water)
- Chewing gum (currently used for multi-vitamins).

Non-oral dosage forms used in pediatric populations include:
- Suppositories
- Topicals
  - Transdermal creams and gels
  - Transdermal patches

  - Lip balm applicators
  - Emollient creams
- Injectables
  - IV including antibiotic eluting stents, intramuscular and subcutaneous.

Aerosol delivery forms include:
- Nasal sprays (disliked by children due to irritability, taste, and smell)
- Metered dose inhalers (also disliked due to taste and smell)
- Nebulizers (standard aerosol delivery system used in the United States for children younger than 4, but this is not the case in other countries)
- Dry powder inhalers (breath actuated inhalers that require a certain rate of inhalation to properly disperse the product).

Dr. Kelly said that the primary issue with drug development for aerosol delivery is particle size, which determines where the drug is deposited in the lung. Most manufacturers try to optimize to 2–5 microns in the conducting airways. For drugs that need to get into the alveoli, a much smaller particle size is needed. Everything that is known about particle size is based on adult data, and there are significant differences between adult and child airway diameter and alveoli size. Dr. Kelly suggested that particle size of smaller than 2 microns may be needed for efficient drug delivery in infants and children.

Jet nebulizers have been used for years. They require spontaneous breathing which children will do as long as it is palatable. Spacer devices are used off label in children younger than 5 years old. They require a tight seal causing discomfort.

Dr. Kelly presented the mean peak inspiratory flows in children:

Age group	**Diskus**	**Aerolizer**	**Turbuhaler**
2	29.2 (4.1)	30.5 (6.1)	20.2 (2.8)
3	43.8 (17.1)	44.7 (10.3)	37.9 (26)
4	41.6 (14)	51.1 (20.9)	35.0 (15.8)
5	51.1 (15.6)	54.6 (18.3)	44.6 (23.1)
6–9	58.5 (18.7)	65.5 (27.6)	39.7 (13.2)
10–12	58.6 (22.7)	75.0 (28)	47.9 (15.6)

He pointed out that for peak inspiratory flow, 60 L/min is optimal, but only two out of ten 2-year-olds and about half of 3-year-olds can do this. The lung dose for dry powder inhalers are:

Turbuhaler®
- Adults 20–30%
- Children
  - 3–5 years 13.4% (n=2)
  - 6–8 years 29.6% (n=6)
  - 9–12 years 24.4% (n=6).

(Devadason et al. Eur Respir J 1997;10:2023-2028)

Dr. Kelly said that the turboinhaler has no taste so it is generally accepted by adolescents.

Diskhaler ® and Diskus ®
- 11-15%.

The large variability in the dose delivered by these dry powder inhalers creates a regulatory issue. Dr. Kelly said that if a mask is moved 2 cm away from a child's face, less than 50 percent of the drug dose is delivered.

Other issues for pediatric inhaled formulations are:
- Taste/smell
- Airway irritability/tolerability
- Excipients (safety, metabolism)
- Packaging.

Some issues for pediatric devices are:
- Intuitive to use
- Ease of cleaning
- Durability, lifespan of device
- Patient feedback about success of dosing
- Reproducibility or variability of dose
- Efficiency
- Nominal dose versus device efficiency (open devices)
- Expected treatment duration
- Mouthpiece design
- Mask design and fit
- Infants: device design to avoid fussiness or crying
- Cost
- Instructions for use and cleaning.

Dr. Kelly ended his presentation by explaining that aerosol delivery systems have marked variability of doses because they are dependent on the cooperation of the child.

Dr. Giacoia asked the chairs of each group to come to the front of the room to answer questions from participants.

Dr. Kelly was asked if airflow is proportional to the radius or diameter of the tube. The roles of particle delivery and laminar flow in aerosol delivery were also raised. Dr. Kelly replied that he is a pharmacist, not a physiologist, but his understanding is that resistance decreases as the size of the airways increases. He added that not much is known about aerosol delivery in children because studies have not been done, but more efficient delivery systems for children need to be developed.

The participants discussed criteria for prioritizing formulations to develop. Dr. Kelly said that the primary issue is how many children require the drug. Others said that prioritization should start with evaluation of the dose and disease state. It was noted that the dose drives formulation development because not all drugs are amenable to different dosage forms (for example a 500 mg dose cannot be provided transdermally). Drug delivery may need to be considered separately from drug development. Dr. Thompson added that every time one titrates down due to decreased age, a new formulation needs to be developed.

Dr. Giacoia was asked if the group focus should be on formulations for the United States or the world, and he replied at this point the focus should be on U.S. needs. A participant asked how pharmacists are trained to make extemporaneous formulations, and he was told that the next morning's presentation would address that issue.

The effect of adding flavor (dilution) on dose was raised. Dr. Thompson said that for a class 1 compound, the risk was low but for a class 4 compound, "you are playing with fire." It was noted that flavors manufactured by different companies may affect stability of the same drug differently, and the participant asked how that could be regulated. The speakers agreed that this does happen, and they discussed whether formal stability studies for extemporaneous formulations should be required.

A related topic of discussion concerned the linkage between the quality of a formulation and bioavailability. There is good evidence that particle size affects bioavailability, so standards for extemporaneous formulations should include specifications that the correct dose is delivered. This raised the question of who would develop and enforce these standards. Another participant replied that extemporaneous formulations made in pharmacies are regulated by state boards of pharmacy, and it is not a federal government responsibility. A participant countered that thousands of extemporaneous compounds are made daily in the United States, and the issue is how to regulate them to protect children. He said they he once visited several children's hospitals and made lists of the drugs compounded daily, and the list was 4–5 pages long for each hospital pharmacy.

The discussion moved on to the difficulty of using healthy children in studies of pediatric drugs, and the small numbers of ill children available for studies (for instance, pediatric AIDS). A question was raised as to whether the FDA would accept data from overseas or would allow compilation of data from different companies to allow statistical power.

The chair of the taste group was asked to include in the group breakout discussions the challenge of making medicines palatable for children without creating an "attractive nuisance" that might

increase the risk of poisoning. Dr. Mennella also raised the issue of how applicable taste testing done with healthy children was for medicines used for sick children, because evidence showed some degree of disturbances in taste and smell in ill children. Another participant asked if research had been done on precursors or chasers to mask taste of bitter drugs.

It was noted that there are two routes of approval for developing formulations for off-patent drugs: 505(b)(2) and ANDA with a suitability petition. Because no exclusivity is available in these regulatory routes, there are no incentives to develop pediatric off-patent drugs.

Dr. Mattison referred working group chairs to the guidance for breakout sessions that was provided in the packets, and he reminded participants that the first breakout session should focus on short-term planning. Another document was provided for each group that lists objectives and suggested areas for consideration. Participants moved to one of the four breakout sessions.

Working Group Summaries

After the breakout sessions, participants reconvened to hear summaries from the chairs of each of the four subgroups.

Economics Working Group

Chair: Kathryn McFarland, Ph.D., Abbott Laboratories
Facilitator: George Giacoia, M.D.

Identify economic barriers to development of pediatric formulations and propose solutions to overcome these barriers (costs and benefits):

- Public policy
- Funding/incentives
- Profitability
- Partnerships
- Roles
- Regulatory pathways/orphan drugs
- Smalls, diverse populations (special pediatric needs, titration)
- Risk management.

Review the areas for consideration and recommend any changes that may help achieve the objective(s):

- Determine value of market (include Europe)
- Reduce cost/risk/time to market (meet with FDA to explore perception of areas of flexibility)
  - Expedited review, queuing, filing fees, suitability petition, review times
  - Uniformity of approach to PK with Europe
  - Global standards to increase market
  - Mechanism to import approved pediatric drugs among countries
- Medical need
  - Survey of hospital pharmacies
  - Identify most viable candidates based on unmet need and demand

- Not for profit
  - Context of regulatory risk
  - Vaccine model
- Public awareness
- Intellectual property
- Availability of "existing" formulation
  - Donate NDA to not for profit for tax benefit
  - Pediatric formulation only?
  - Regulatory relief
- Mechanism to test stability for compounding (<30 days)
- Consortium risk sharing
  - Pilot for 2–3 compounds to demonstrate benefit
- PREA/BPCA renewal and extension to off patent for exclusivity
  - Prepare for 2007
- Europe= essentially similar.

The group developed a short-term action plan for achieving the objective(s):
- Reduce cost, risk, and time to market
- Meet with FDA to explore perception of areas of flexibility
  - Expedited review, queuing, filing fees, suitability petition, review times
  - Uniformity of approach to PK with Europe
  - Global standards to increase market
  - Mechanism to import approved pediatric drugs among countries
- Evaluate medical need
  - Survey of hospital pharmacies
  - Identify most viable candidates based on unmet need and demand
- Identify most viable candidates based on unmet need and demand PREA/BPCA renewal and extension to off patent for exclusivity with pediatric BA/BE
  - Prepare for 2007.

In response to the instruction to review the list of proposed deliverables for relevance, identify gaps and prioritize areas for consideration, the group proposed the following:
- Conduct a hospital pharmacy survey to identify priority list containing high use and high unmet need of extemporaneously compounded medications.
- Review and prioritize a list of approved, off-patent drugs with pediatric formulations that are not currently marketed based on market and unmet need.
- Review current regulations and make suggestions for changes to PREA and BPCA.
- Review vaccine initiative to look for structures that may be available to support pediatric formulation development to donate pediatric formulations without risk to adult label.
- Create incentives for PREA and BPCA to encourage formulations of prioritized drugs that are currently widely extemporaneously formulated.
- Create standards for extemporaneous formulations, for instance, Compendia.

Questions and Comments. One participant suggested that safety issues be incorporated into the prioritization scheme. For instance, if the compound is not used frequently but has high risk to

children because of the way it is made or how it is used, it should be high on the list. Identifying these risks can help save children's lives. Dr. Thompson asked if only a bioavailability study was done, how would one know what dose is appropriate. Dr. Bruss responded that PK is needed for the BA/BC, and he also discussed the possibility of getting additional exclusivity for doing safety studies.

Scientific Working Group
Chair: Karen Thompson, Ph.D.
Facilitator: Donald Mattison, M.D.

Dr. Thompson began her summary of the scientific group breakout session by noting how much was accomplished during this face-to-face meeting. She explained that the group agreed that the endpoint of developing formulations is clinical use (with trials that support dosing, safety, and efficacy). Throughout the discussion, the issue of safety for children was stressed.

Some of the regulatory topics discussed included:

- The Food and Drug Administration Modernization Act Section 111, which provides available data on pediatric use. Need to determine dose, safety, effectiveness, and then develop commercial formulations that can be evaluated in relevant pediatric populations to characterize clinical utility.
- Two paths—new drug entities versus off-patent. Participants noted that clinical uses drive NCE, but formulations drive off-patent.
- Because BPCA is pushing the NIH into pediatric drug development, who will be responsible for the formulation over time? If the NIH is going to focus on development and licensing of products, will it provide the infrastructure needed? Are existing NIH networks available for testing newly developed formulations?
- Need standards for extemporaneous formulations, including vehicle classification systems to characterize and describe stability, solubility, taste, texture, packaging, bioavailability, and bioequivalence.
- Difficulties of using children in bioequivalence and bioavailibity studies.
- BCS classification, adapted for children.
  - Compounding pharmacists have short time to prepare
  - Commonly used commercial vehicles (API—USP powder or commercial)
  - Range of commercial vehicles with specific characteristics
  - Class I may work but must be looked at because of smaller volumes used in children (250 mg/250 mL, 1 mg/mL, may be considered a boundary?)
  - Class II and III may require more consideration
  - Class IV may need more discussion.
- If commercial formulation is not available then test extemporaneous formulation and publish extemporaneous formulation on label.
- Should compounding-manufacturing centers, similar to those in the United Kingdom, be created? Should the FDA be involved?
- An NIH/FDA group currently meets to prioritize drugs to be studied. The list includes several hundred drugs based on the number of prescriptions written.

Discussion included labeling issues, such as:

- If pediatricians followed only approved "labels," they would have no drugs to work with because much is known that is not on the FDA-approved label. Codify and solidify clinical and research information so that it can be used.
- How do practitioners know how to use the drugs appropriately? There are different practices, different combinations, different endpoints, and regional differences.
- Check with practitioners/clinicians to see what drugs are problematic and need to be studied further, with the idea of altering the label and adding pediatric indications.
- Labeling needs a multi-pronged approach based on identifying the problems and then deciding what needs to be fixed first.

The group also discussed how essential partnerships are to this project and the need to identify creative ways to accomplish NIH, academic, clinical, and industry (including global partners) goals and encourage or invest in academic-industry partnerships.

The group discussed the urgent need to compile information:

- Compile listing of commercial vehicles and APIs.
- Should the USP serve as a repository of product characteristics to allow rational formulation?
- Should USP monographs serve as a formal standard?
- Should USP labs do stability testing of specific preparations, packaging, dosing testing (dropper) using validated analytical methods?
- What is the impact of excipients on analytical methods?
- List the analytic methods to describe the characteristics of the various formulations under consideration (FDA has information on various formulations as part of product development information submitted).
- Provide data from pharmaceutical industry to USP so that it can be used in official compounding monographs.
- How can industry liability be limited or negated if they release information to public for use by professionals?
- Send a survey concerning pediatric and geriatric formulations to several hundred pharmacists to obtain information which will then be prioritized.

Special issues included:

- Legal responsibility for shared information.
- The need to establish incentives for pediatric formulation development.
- The need to evaluate risks versus benefits when changing standards of safety and efficacy.
- The use of preservatives in pediatric formulations, especially in those used in neonates.
- The use of non-aqueous vehicles.
- Permeability based on CACO-2 cells and human perfusion studies.
- Who is going to pay for all of this? Foundations? Government?
- Identify "low hanging fruit," what is available and useful but requires minimum resources.

The scientific group developed a list of recommendations to meet short-term goals:

- Identify financial incentives to develop pediatric formulations for patent and off-patent drugs.
- Focus on the highest unmet need(s).

- Identify entities that may be interested in funding the necessary aspects of these unmet needs.
- Resolve barrier(s) to sharing information.
- Resolve barriers to development of pediatric formulations (commercial versus extemporaneous). Development can also include increasing the "availability" of new products, better labels, and more.
- Reexamine the utility of the teleconferences considering how much work was accomplished by the group during the in-person meeting.

Questions and Comments. Dr. Tuel raised the issue of possibly dovetailing U.S. scientific standards with EU standards to allow development of model PK studies that all parties can use. Another participant asked if the group had discussed determination of pediatric doses, volume of distribution, and whether permeability changes with age. Dr. Bruss asked if a company did the science and obtained approval for a formulation, who would manufacture, do stability testing studies, and distribute? Dr. Thompson replied that most of the discussion was on obtaining data, not market development. Dr. McFarland asked about universal standards for extemporaneous compounding to allow for standard recipes and best practices.

Taste and Flavor Testing Working Group

Chair: Julie Mennella, M.D.
Facilitator: Barry Davis, Ph.D.

Dr. Mennella presented the results of the taste working group discussions. The participants' overall view was that more research on the ontogeny of the chemical senses in humans will enable them to determine how children are similar and different from adults in both sensory perception and physiology. Genomics and other cellular and molecular studies on taste may provide the tools for major advances in the understanding of the sensory systems which, in turn, may lead to discoveries of new technologies that mask or block the tastes, irritants, and odors that make oral pharmaceuticals unpalatable to children.

Deliverables that could be created by the group include:

- A document that summarizes the peer-reviewed scientific literature on the ontogeny of taste, smell, and chemical irritation from both a behavioral and physiological perspective. It would also include a review of case studies and peer-reviewed literature on how these senses are modified with disease state, illness, and medication use. The document would take a lifespan approach and the review on adults would also include the elderly.
- Identification of gaps in knowledge and prioritization of research needs in the scientific areas of taste and flavor.
- Evaluate drug palatability as it relates to bitter taste, flavors, irritants, and grittiness as a function of developmental age. The consensus was the priority is bitter taste. Much discussion focused on several issues related to bitter taste. Are all bitter compounds the same? Bitter is a common percept; some compounds are not just bitter but sour and irritating; there may be different developmental pathways (for example, urea sensitivity develops postnatally). What about other bitters? Is there a universal bitter percept and if so, how does it change with age? How much of a bitter block is needed? It varies on dose-response curve. If one can wipe out 99 percent of bitterness, can flavor masking deal with the remaining 1

percent? If the bitterness lingers, this magnifies the challenge. It was reported that it is easier to deal with short duration bitters with current technologies. What makes some bitter compounds linger (for example, Bitrex)? Does it deal with the chemical attributes of compounds? On/off rates of the receptor? Partitioning in the membrane and strength of binding? One strategy would be to look for broad acting bitter blockers that act on a downstream site of the receptor. If one can block one or another of the common elements, one can theoretically block all of the bitter tastes.

- Critique appropriateness of current pediatric tests and measures (for example, hedonic scales, facial expression) and determine what tasks are appropriate for what ages with the ultimate goal of facilitating such research by pharmaceutical companies. The group's goals are to determine:
  - What research is needed to demonstrate validity and predictive value of findings gleaned from such tests?
  - When should adult panelists be used versus children? Identify the ethical issues in testing oral pharmaceuticals on healthy and sick children.
  - Include measures on parental perceptions as they relate to taste issues and how this affects parental and child compliance.
  - Develop scales or questions that could be included in clinical trials that address taste-related issues on child acceptance, parental perceptions, and compliance.
- Much of the research published to date has focused on behavioral responses to taste and flavors and the differences between children and adults. The extent that these differences reflect physiological differences in children and adults is a subject for further investigation. Conversely, what are the physiological similarity in taste responses in children and adults? Is there any evidence that mixture suppression works in infants like it does in older children and adults? Does mixture suppression work differently in children when compared to adults?
- Identify what flavors are preferred from a cross-cultural perspective. Can there be a single formulation that can be accepted by everyone (sweet taste, orange flavor)? Peer-reviewed cross-cultural odor and flavor studies are needed.
- Document the problem. Identify and document the following for children as a function of their age, whether their illness is acute or chronic, and their dosing frequency:
  - How many children refuse medicine because of its taste?
  - How often do taste issues impact upon drug compliance and adherence to therapy?
  - Are there more compliance issues due to taste in generic brands of medicines when compared to innovator branded products?
  - With more frequent dosing, does medication interfere with meals?

The areas for consideration for the group and any changes that may help achieve the objective(s) include:

- Establishment of strategies for sharing. Try to develop a partnership and data sharing plan among academics, government, and industry to gain access to existing, yet proprietary, data on taste masking, bitter and irritant blocking, and drug palatability to determine what approaches have been successful and what are the major obstacles related to drug palatability for pediatric populations.
- Electronic tongue/nose technologies and expression of concerns and doubts on how this technology can be applied to the large individual differences in bitter taste perception. This

technology is still in its infancy and holds significant promise, which requires further investigation. However, concerns were raised about its applicability related to pediatric drug palatability issues. First, such technologies are not based on biological principles. Second, they are used as detectors but not for sensory evaluation. The group's consensus was that this technology is currently not useful. They would rather see investment in research on receptor and cellular assay systems for bitter taste and on human psychophysics.

A short-term action plan (in early 2006 and thereafter, if applicable) for achieving the objective(s) includes:

- Assess the current state of knowledge and develop a document that summarized the ontogeny of human taste, smell, and chemical irritation and how these senses are affected by disease and medication use.
- Identify and prioritize research needs related to the ontogeny of bitter taste perception in humans.
- Establish whether current taste test methodologies used in children are acceptable, reliable, and predictive of initial acceptance and long-term compliance. Methodologies should be evaluated for a number of different age groups to determine what methods are valid for what age groups and how the procedures need to be modified for younger children. Survey pharmaceutical companies and determine what age groups of children are they most interested in evaluating acceptance of oral pharmaceuticals.

Other issues include:

- The question was raised in the group discussion on whether palatability should be required for FDA approval.
- Safety issues if medicine is too palatable; how does one balance this?

Review list of proposed deliverables for relevance; identify gaps; prioritize areas for consideration:

- Provide literature review on current state of knowledge in the ontogeny of the chemical senses and how they are modified with disease state and medication use. Document the extent of the taste problem. Identify and document the following:
  - How many children refuse medicine because of its taste
  - How often do taste issues impact upon drug compliance and adherence to therapy
  - Are there more compliance issues due to taste in generic brands of medicines when compared to innovator branded products?
- Such data are needed for children as a function of their age, whether their illness is acute or chronic, and dosing frequency. With more frequent dosing, does medication interfere with meals? Are there companies (INS) that have such databases?
- Survey pediatricians, parents, or industry to obtain data on both initial acceptance and long term compliance.
- Establish data sharing plan.
- Identify the current taste methodologies used for pediatric populations in industry and basic research. Establish whether current taste test methodologies used in children are acceptable, reliable, and predictive of initial acceptance and long-term compliance. Testing methods

need to be evaluated for a variety of age groups to determine what methods are valid for what age groups and how the procedures need to be modified for younger children.

- Identify questions that can be incorporated into clinical trials to systematically evaluate some of the taste issues as well as parental perceptions and biases. Survey industry to find out what age child they want to test.
- From an industry perspective, is there a need to establish guidelines on the minimal amount of toxicology and side effect information that is needed before you can do taste tests on infants and children? Does one have to file an IND to test all the different flavors? Does this change with therapeutic compound? Can pharmaceutical companies make a base formulation (that is sweet) and then have the doctor, based on the child's preference, script what flavor should be added? Then one would have to provide 14-day stability data (would be easier to do than 2-year data).
- One research priority is on the receptor and cellular assay systems underlying bitter taste. For example, characterize the developmental variation in the expression of the 25 human bitter taste receptors. When are they expressed during ontogeny and senescence? Is there a difference in expression during ontogeny? If so, does difference in expression relate to individual differences in bitter taste perception? How does expression change with disease state? Medication usage? Are there other bitter taste detection mechanisms that do not use these receptors? Do they occur early in ontogeny and diminish with age?

Questions and Comments. Dr. Mennella was asked about a universal flavor. She said that possibly a universal base formulation made from a balance of the 4–5 basic tastes might be possible. Individual flavors based on cultural preferences could them be added. She was also asked about Flavorx and other flavor technologies. Dr. Bruss suggested adding taste panels as a part of regulatory approval. Because some generics taste far worse than the brand name medications, the group discussed whether taste should be a criterion used in developing generics.

Dr. Mennella was asked who would be responsible if a flavor added to a formulation adulterated the product. A participant said that adulterating an unapproved product (extemporaneous compound) just resulted in another unapproved drug. Dr. Nunn remarked on the potential advantages of using the electronic nose and tongue for quantitative analysis, especially for cytotoxic drugs that cannot be tested in other ways.

Dr. Giacoia asked about the best mechanism for obtaining data from pharmaceutical companies. Responses included:

- Data from clinical trials available on www.clinicaltrials.gov
- Information listed on patent application
- Much information is proprietary and not available.

New Technologies and Drug Delivery Systems

Chair: H. William Kelly, Pharm.D.
Facilitator: William Rodriguez, M.D., Ph.D., Center for Drug Evaluation and Research, FDA

Dr. Kelly said that the group discussions focused on a review of available technologies. Future activities included:

- Looking at the list of drugs and providing suggestions for the technologies that could be used (the ones the ones that are currently available and feasible
- Developing collaborative proposals with the industry and other stakeholders
- Writing a position paper.

The group's short-term objectives include:
- Considering the impact of newer technologies
- Applying already available technologies to pediatric formulations
- Identifying partners.

The areas for consideration included:
- Focus on readily available technologies such as oral liquids, ODTs, TDDS, and preparations for respiratory delivery
- Match APIs with technologies.

The short-term action plan items were:
- Meet again
- Participate in conference calls—"virtual company of ideas and proposal"
- Develop a template protocol for matching drug, technology, and indications—and prioritize them.
- Recruit members from industry and academia with expertise in emerging technologies.

Proposed deliverables included developing a position paper. After matching and prioritization, newborn and infants will be emphasized per the BPCA. Toddlers and others will also be included.

Day 2

Dr. Giacoia welcomed participants to the second day of the conference. He said that the discussions would focus on prioritization of pediatric formulations and he introduced the first speaker, Dr. Walson.

Scope of the Problem: Need for Prioritization

Philip D. Walson, M.D., Professor of Pediatrics, University of Cincinnati; Director, Children's Hospital Office of Clinical Trials; Editor-in-Chief, Clinical Therapeutics

Dr. Walson said that prioritization is needed prior to developing formulations of drugs used in pediatric populations. Clearly, priorities are different for a company deciding how to invest time and money than they are for government. Dr. Walson explained that his presentation is aimed at the various government entities (FDA, NICHD) that recognize a problem and are deciding how to address it. Dr. Walson said that one thing has changed since 1998 when he spoke at the Boston workshop on this topic—the desire to solve the problem has grown.

Dr. Walson explained that the topic for his talk is: If money is available to develop formulations that the pharmaceutical industry has not, can not, or will not develop, how would one rank those

drugs? He said that this issue brought to mind a quote, "There is no limit to what you can do if you don't mind who gets credit for it."

To prioritize pediatric formulations, one must begin with the following questions:
- How difficult is it to give a patient one dose of a particular formulation of a specific product? Answers will form a continuum from impossible (or dangerous) to easy. If easy, the need to spend money to develop a new formulation decreases.
- If impossible, is there another formulation of this drug or a similar drug that can be used?
- What happens if the patient does not take every dose?

Other aspects of the problem to consider are:
- Populations. What is the scope of the problem?
- Individual preferences. For example, a seaweed flavored antibiotic that is popular in Japan probably would not be as popular with children in the United States.
- Alternative solutions. If it is easy to grind and sprinkle, why develop a new formulation? Are effective products already developed and approved in other countries?
- Limited funds.

As for populations, Dr. Walson suggested considering the following:
- Number (patients, scripts, doses). These data are not easy to get, but a measure of the problem is necessary in order to prioritize.
- Types of formulations (IV, drops, liquids, wafers, dry powders).
- Condition severity and chronicity. For instance, less money and time should be spent on mild problems than on life threatening conditions.

The following issues about alternative options should also be considered:
- Similar or alternative treatments. Does a product exist that performs the same function? Has a formulation that works been tested in a pharmacy, hospital, or at a pharmaceutical company? If a company already has developed a formulation that for whatever reason is not marketed, can those data be shared?
- Extemporaneous products. Extemporaneous formulations can be dangerous if made improperly. For instance, oncology nurses at some children's hospitals use the same mortar and pestle to grind various pills without adequate rinsing. Dr. Walson said he would not want his antibiotic to be mixed in a container that was just used to crush methotrexate.
- Global products. Dr. Walson believes that the United States should use appropriate formulations developed in other countries before spending large amounts of money doing something that has already been done. He also stressed the need to address cultural differences, including Americans' aversion to using some types of formulations, such as suppositories, that are widely used in other countries.

To help determine the cost and practicality of developing a formulation, one should learn of any prior attempts to make it. If a company has attempted several versions of a formulation and knows what does not work, do not waste money trying to do it again. Evaluating practicality of a formulation also includes determining shelf life and the toxicity of excipients.

Dr. Walson's proposed prioritization scale is based on scoring (weighting) various items including:

- Whether the formulation is for hospitalized or nonhospitalized children
- Measure of volume of doses being formulated currently (either frequency being compounded, number of doses, patients, prescriptions, or a combination)
- Severity of condition graded on a 1–3 scale (life-threatening, severe, or minor)
- Available alternative, pediatric-appropriate formulation of a similar ("me-too") drug, another drug in same class with similar efficacy and tolerability, or a validated extemporaneous product
- Economic costs of compounding, developing, and dispensing (including nonmonetary items such as lives lost).

Dr. Walson then asked if participants had any additional measures to include in the scheme. He said that determining the weights for each item needs to be done and determining who will rate them has yet to be determined. Then the list of products will be ranked and a decision will be made on which formulations will be developed first. He invited listeners to share suggestions or comments on the Web site (www.circlesolutions.com/BPCA, click on Scientific, Technical, and Regulatory Challenges for the Development of Pediatric Formulations (Scientific WG), click on Additional Documents, click on Proposed Items for Prioritization System Dr. Walson).

Questions and Comments. Dr. McFarland mentioned the costs of evaluating efficacy and conducting clinical trials of new formulations in pediatrics. Dr. Walson responded that if there is no alternative product and the drug has been shown to work in another population, it would help to invoke the 1994 Pediatric Rule by showing that it is similar and not do the efficacy trials.

Dr. Bruss said that there are certain required steps in the approval process for new products. Dr. Walson agreed that this was true; however, not being from the FDA or industry, it does not make sense to him. If a product is being used for a life threatening condition, the first step is to develop a formulation to test. The label decisions and marketing factors are a different issue. He suggested changing regulations to allow a formulation to be developed for drugs already being used.

A question was asked about the importance of stability of new formulations. Dr. Walson responded that many current extemporaneous formulations pose a public health threat to children. For example, he said if a company knows how to make a stable liquid form of a drug, they will say the FDA will not let them divulge the data on how to produce it, even when everyone knows that less stable or safe forms of the drug are being extemporaneously produced. Dr. Walson suggested changing the law to allow access to the data so that safe products can be produced.

One of the members of the scientific subgroup said that one of the difficult issues discussed the previous day was that the need for the product does not always balance the economics. If a large amount of published data exists on an extemporaneously produced product, one can do a literature search. That product would get a higher priority than a product a company wishes to register and on which there are no data. Experimentation and development are enormously

expensive. He said Dr. Walson's presentation did not reflect economic reality. The total developmental needs versus costs to meet those needs is a fundamental consideration. Dr. Walson accepted his point and added that perhaps the money should not be spent on developing and testing formulations but on finding formulation information and publishing it.

United States Pharmacopeia Past and 2006 Survey

Loyd V. Allen, Jr., Ph.D., R.Ph., Editor-in-Chief, International Journal of Pharmaceutical Compounding; Chair, USP Expert Committee on Pharmacy Compounding

Dr. Allen opened his discussion by explaining that the role of the compounding pharmacist is to provide individualized therapy. However, pharmacists can do nothing without a prescription from the physician. If the prescribed medication is not commercially available, the compounding pharmacist can prepare it. Some of the reasons for the growth of pharmacy compounding in recent years are:

- Limited dosage forms
- Limited strengths
- Home health care
- Hospice
- Orphan drugs
- Veterinary compounding
- New therapeutic approaches
- Nonavailable drug products/combinations (including discontinued drugs, drug shortages).

He said that more than 7,500 drugs have been discontinued from the market in the last 25 years. Growth of pharmacy compounding has also been fueled by growth in special populations including:

- Pediatrics
- Geriatrics
- Bioidentical hormone replacement therapy
- Pain management
- Dental patients
- Environmentally and cosmetic sensitive patients
- Sports injuries
- Veterinary compounding (small, large, herd, exotic, companion).

Pharmacy compounding has been divided into seven categories:

- Nonsterile simple (graduate from a pharmacy college can do)
- Nonsterile complex (bulk drug substances requiring exhaust systems and complex calculations)
- Sterile—low risk (three or fewer sterile ingredients combined to make a product)
- Sterile—moderate risk (more than three sterile ingredients, total parenteral nutrition [TPN] solutions)
- Sterile—high risk (uses nonsterile ingredients or nonsterile equipment with terminal sterilization)
- Nuclear pharmacy

- Veterinary compounding.

Dr. Allen next provided estimated compounded prescription sales in 2000 (source—consulting research organization that had discussions with industry personnel and project consultants).

Independent community pharmacies:
- 22,000 pharmacies
- 35,000 compounded prescriptions per pharmacy
- $3,360,000,000.

Non-independent community pharmacies:
- 32,500 pharmacies
- 57,000 compounded prescriptions per pharmacy
- $1,896,000,000.

Hospitals/institutions/regional infusion centers:
- 12,000 pharmacies
- 57,000 compounded prescriptions per pharmacy
- $3,000,000,000.

Estimated compounded prescription sales in 2000:
- 66,000 pharmacies do some compounding
- 50,000 prescriptions per pharmacy
- $8,535,000,000 total compounded prescription sales revenue.

According to the National Community Pharmacists Association Journal (November 2005), approximately 70 percent of pharmacies report doing some compounding. Pharmacy compounding oversight is provided by:
- Pharmacy State Boards
- Individual state laws
- Food and Drug Administration.

Pharmacy standards include:
- U.S. Pharmacopeia
- Occupational Safety and Health Administration (OSHA)
- Environmental Protection Agency (EPA)
- Drug Enforcement Agency (DEA).

Quality initiatives include:
- USP general chapters
- USP standardized monographs
- Pharmacy Compounding Accreditation Board
- Educational initiatives (colleges of pharmacy are remodeling or creating new laboratories)
- North American Pharmacy Licensing Examination (NAPLEX)
- State Board of Pharmacy Initiatives

- FDA-registered laboratories.

Dr. Allen noted that questions concerning stability had arisen several times during the meeting. He explained that beyond-use dates are applied to compounded preparations, but expiration dates are used for commercially prepared products. In the absence of valid stability information, the following maximum beyond-use dates are recommended, provided that the preparations are packaged in tight, light-resistant containers and stored at control room temperature unless otherwise indicated.

Nonaqueous liquids (for example, oil) and solids:
- If a manufactured drug is the source, not later than 25 percent of time remaining until product's expiration date or 6 months, whichever is earlier
- If USP or NF substance is source, not later than 6 months.

Water-containing formulations prepared from solid ingredients:
- Not later than 14 days when stored at refrigerated temperature.

All other formulations:
- Not later than the intended duration of therapy or 30 days, whichever is earlier.

Two different levels are used for sterility—preparations that require no sterility testing and those that need to have sterility testing done.

Low-risk preparations that require no sterility testing can be stored as follows:
- Room temperature≤ 48 hours
- Refrigerated ≤ 14 days
- ≤ -20° C or colder ≤ 45 days

Medium-risk preparations requiring no sterility testing can be stored as follows:
- Room temperature≤ 30 hours
- Refrigerated ≤ 7 days
- ≤ -20° C ≤ 45 days

High-risk preparations requiring no sterility testing can be stored as follows:
- Room temperature≤ 24 hours
- Refrigerated ≤ 3 days
- ≤ -20° C ≤ 45 days

If the pharmacist does sterility testing—for low, medium, or high risk preparations—the beyond-use dates contained in USP chapter 795 are used.

Dr. Allen explained that analytical methods that are increasingly used in pharmacies or that are outsourced to contract laboratories include:
- Melting point
- UV/vis/IR spectroscopy

- High performance liquid chromatography (HPLC)
- Gas chromatography (GC)
- Sterility
- Endotoxin
- Weight
- Volume
- Macro/micro
- pH
- Osmolality
- Refractive index
- Specific gravity.

Dr. Allen began his brief history of compounding in U.S. pharmacies by saying that the USP has been setting drug standards since 1820. In the 1900s, the USP reoriented to drug manufacturing. In the 1940s, approximately 40 percent of prescriptions were compounded. From the 1950s to the 1970s, however, more than 99 percent of drugs were manufactured rather than compounded. Compounding began to increase in the 1980s and has continued to do so. As a result, today the USP must meet the needs of both manufacturers and pharmacists. In July 2005, a new edition of the USP Pharmacists' Pharmacopeia was published that contains an official section and an authorized section (supportive information for pharmacy compounding).

The USP became reinvolved in compounding after resolution #4 was passed by delegates in 1985. In 1990, an expert advisory panel on compounding was established to write general chapters and to develop compounding monographs. In 2000, a resolution was passed that established two pharmacy compounding expert committees for:
- Nonsterile compounding
- Sterile compounding.

During the 2000 convention, a resolution was passed to continue to develop and institute, in collaboration with other organizations as appropriate, specific initiatives focused on the development of appropriate compounding guidelines and monographs for noncommercially available, but commonly prescribed, medicines and dosage forms for use in special populations, notably neonatal, pediatric, geriatric, and terminally ill patients. In August 2000, a survey of pharmacists in hospitals, community pharmacies, and long-term care facilities identified more than 150 preparations, mostly pediatric, that need official monographs in the USP including stability studies. A 2001 survey listed over 1,000 preparations needing monographs. Dr. Allen said that more than 5,000 different formulations are being compounded every day in the United States.

Recent USP activities involving pediatric compounding include:
- Developed more than 150 official compounding monographs (includes a formula and beyond-use date)
- Plan to add 50 new monographs per year (which require stability studies)
- Included four official compounding chapters
- Creating one new chapter on quality issues in compounding pharmacy (in process).

Dr. Allen pointed out that many other USP chapters also apply to pharmaceutical compounding. He said that the USP has agreed to do an additional survey in 2006 and working copies were discussed at this meeting. Two separate surveys, one on pediatric patients and one on geriatric patients, were sent to participants in the mail prior to the meeting. A number of lists have also been distributed, and after the survey is complete in the first quarter of the year, prioritization can commence.

Questions and Comments. In response to a question on standards, Dr. Allen said that every compounding pharmacy is required to have a series (approximately 250) of standard operating procedures. These address issues such as cleaning and rotation of disinfectants, but perhaps not to the same degree as is required in industry.

Dr. Tuel asked Dr. Allen about the view that compounding pharmacies do not have the volume to conduct long-term sterilization studies. Dr. Allen replied that it is true that they do not validate for long-term use because the preparations are not compounded for long-term use. However, the beyond-use dates are quite short. He added that not every preparation is tested for sterility because individual patients are waiting for their prescriptions.

Dr. Walson mentioned the power of USP official status, noting that insurance companies are required to pay for those compounded products. He said because 150 monographs are available, time should not be spent developing new formulations for them. His second point concerned geriatric products. He suggested including handicapped adults or any adults who have trouble swallowing, rather than using the term "geriatric."

Dr. Allen said that 85 new formulas are in line for stability studies, in addition to the 150 that are already in the USP. He was then asked how many of the 150 formulations are for pediatric populations. Dr. Allen replied at least 80 percent.

Dr. Allen was then asked to explain FDA-approved laboratories that he mentioned in his presentation. He replied that many compounding pharmacies now contract with FDA-registered laboratories also used by the pharmaceutical industry to do sterility, potency, and endotoxin testing.

According to Dr. Giacoia, listing and prioritization are essential to the PFI initiative, and each subgroup has been exploring this topic. He reminded participants that it is the beginning of the process and encouraged each subgroup to include issues of listing and prioritization in their discussions.

Goals for Day Two "Future Steps"

Donald R. Mattison, M.D.

Dr. Mattison said the summaries from the previous day's breakout sessions included a fair amount of overlap and highlighted central issues:

- What products are compounded for pediatrics

- How to identify gaps in knowledge and unmet needs
- Sharing strategies among academic, federal, and industry partners
- Current FDA regulatory structure
- Opportunities for improvement.

The short-term planning needs of NICHD were met by the breakout discussions during the first day of the working meeting. The next breakout sessions should focus on longer-term needs (12–18 months or longer) and plans. Dr. Mattison referred to the guidance papers provided in the packet that outlined topics for the breakout sessions on future planning for the PFI:

- Discuss deliverables or products that would evolve from the PFI
- Discuss action items for longer-term objectives, including future workshops, colloquia, creation of new working groups for targeted objectives, literature reviews, and identification of research gaps
- Discuss what PFI activities are needed to help prepare for a workshop (conference calls, papers, reviews, templates for study design)
- Propose a plan to gather information to support the development of longer-term deliverables
- Topics for longer-term consideration may include
  - Ethical/legal issues of formulation or bioavailability testing
  - Bioavailability and bioequivalence in different pediatric formulations
  - Design of PK/PD safety studies (scientific and regulatory challenges)
  - Practices of medication handling by health professionals and caregivers
- Global issues of pediatric formulations including educational and information dissemination.

He thanked everyone for their participation and excellent discussions.

Working Group Summaries

After the breakout sessions, participants reconvened to hear summaries from the chairs of each of the four subgroups.

Economics Working Group

Chair: Kathryn McFarland, Ph.D.
Facilitator: George Giacoia, M.D.

Dr. McFarland said that the economics subgroup discussed ways to overcome the economic barriers to creating pediatric formulations. The ideas from the group were to:

- Utilize exclusivity to encourage industry to develop suitable formulations
- Utilize pediatric PK as a basis for exclusivity via bridging from adult data
- Add additional exclusivity for conducting clinical trials (for instance, 5–7 years, analogous to what is done for new chemical entities or orphan drugs)
- Create a tax benefit for development of pediatric formulations (to reduce cost or increase profitability)
- Reduce regulatory barriers
- Accelerate ANDA (which includes suitability petitions) and 505(b)(2) processes to encourage development of pediatric products

- Do a cost analysis of compounding versus developing FDA approved drugs to enable prioritization of compounds (including how cost is charged out by hospitals)
- Establish standards for pediatric palatability (for instance, some generic antibiotics taste bitter. Incentives should require development of products that children will actually take)
- Move the continuum to right: 5,000 extemporaneous products < 150 USP monographs < FDA approved formulation < formulation + clinical trials
- Analyze adverse events and litigation costs/numbers of lawsuits from extemporaneous formulations due to quality issues and impact
- Create mechanisms to license and import pediatric formulations available in other countries (analogous to European regulations on imports)
- Establish regulatory collaboration to make pediatric drugs available globally
- Perform an economic analysis to ascertain why so few pediatric generic formulations are available.

Dr. McFarland explained that two processes were needed—rewarding industry for developing formulations and rewarding them for conducting clinical trials. The goal is not to replace compounding, but to get more products under the regulatory process.

Questions and Comments. Dr. McFarland was asked if the suggestion on exclusivity applied to specific formulations or to those made under BPCA that apply to ranges of products. Dr. McFarland said that exclusivity has been effective for innovative drugs, but the economic subgroup discussion was aimed at exclusivity of off-patent drugs.

Scientific Working Group

Chair: Karen Thompson, Ph.D.
Facilitator: Donald Mattison, M.D.

Dr. Thompson said that the scientific working group's primary concern was prioritization, which can be looked at two ways:

- Evaluate how compounds are currently being used
- Determine when clinical studies need to be conducted.

She suggested creating two lists: (1) formulations that could be developed fairly quickly and (2) ones that will require clinical testing and thus will have a significantly longer development time. The group also discussed utilization of USP monographs as a means to try to standardize some of the preparations being used. She said that monographs are peer reviewed prior to finalization and the standard of practice on which the monograph is based should be reviewed on a yearly basis. Some of the testing listed in the monographs might require closer scrutiny. For example, does the testing specifically designate polymorphs of certain compounds? Some critical tests may need to be added to the monographs to increase confidence. Because monographs are translated into multiple languages, they are a cost effective way to share information.

The group also discussed the 2007 sunsets on legislation and the differences in language between PREA and BPCA. The focus of BPCA is to gather information on data about children rather than developing a commercially viable formulation. Because exclusivity is a "one-shot deal," requests

are being written so expansively that they are difficult for companies to address. The group thought that perhaps a scaling of written request to address exclusivity for different populations would help. Separating the commercial market from the scientific information is important. Reemphasizing the acceptability of an extemporaneous formulation for exclusivity might allow companies to provide information to the USP, possibly leading to a monograph.

Dr. Thompson said that FDA representatives reminded participants that USP's focus is on the physical and chemical characterization of the formulation, but the FDA focuses on clinical data (PK or efficacy studies). Current and future approaches to safety were also discussed.

The group also discussed data sharing. There have been cases in which companies developed formulations, obtained exclusivity, and decided not to market the formulation. Everyone then loses. If a company decides not to market a formulation, developing a means for the company to share their data with the USP might allow monographs to be written for that preparation.

Questions and Comments. Dr. Tuel said that prioritization needs to include economic costs of both development and marketing. For example, if using public funds, those costs need to be factored in. Dr. Walson said that the United States spends enormous amounts on end-of-life care and almost none on children. Dr. Thompson said that the group had discussed whether children affected should be based on worldwide numbers (for example, malaria) or just children impacted in the United States. Dr. Giacoia said that initially the focus will be on formulations for children in the United States.

Dr. Bruss said that any comprehensive prioritization process should include scientific considerations, costs, commercial applications, and regulatory aspects. After all of these factors are evaluated, then a scoring system should be developed.

Taste and Flavor Testing Working Group

Chair: Julie Mennella, M.D.
Facilitator: Barry Davis, Ph.D.

Dr. Mennella presented the results of the taste and flavor testing working group discussions. She said a clear need was to evaluate pediatric taste test technologies in industry and academics to determine:

- What is most effective
- What is most predictive of short-term acceptance and long-term compliance
- Parental perceptions.

She posed several questions:

- From an industry perspective, what is the minimum amount of information needed before taste tests are done for products for children and adults?
- Is it necessary to establish guidelines?
- For example, is an IND necessary before doing taste testing?

Dr. Mennella explained that deliverables or products that could evolve from the PFI include:

- Review of the literature on the ontology of taste perception as well as how perception is altered by disease state and by medication use
- Formalize a data sharing plan
- Review and evaluate methodologies used in industry and academics for taste testing in children and assessing parental perceptions and compliance
- Research initiative on bitter taste (for example, receptor and cellular assay systems; bitter taste physiology and perception in humans during ontogeny; bitter taste knock-out animal models)
- Request a guidance document for industry for taste testing in children (should include basic compound information needed before taste testing can occur in different age groups. What defines palatability/acceptable product? Also discuss ethical and legal issues in testing children)
- Document how widespread taste problems are in children's medications and what parents consider acceptable formulations of medications for children (using surveys, current databases, parental beliefs on use of suppositories)
- Produce a cost-benefit analysis comparing cost and difficulties in blocking bitter taste in liquids versus micro encapsulation or other delivery methods that bypass palatability issues.

To develop an action plan, the taste working group suggests:
- More industry involvement and perspective on the above-mentioned issues
- More involvement of research-oriented pediatricians who have sensitivity to these issues
- Adding a FDA member to the working group.

The subgroup's needs may take longer because it requires basic science and survey research.

To prepare for future workshops:
- Provide a consensus of outcomes from the current meeting
- Determine what type of monetary commitment NICHD has to allow the PFI to move forward especially since some of the activities require extramural research, which requires additional funding (basic research, taste test methodologies in industry and academics, documenting the taste problem).

Questions and Comments. One participant said that his family's experiences while living in France showed that using suppositories in children eliminated fights, spills, and taste problems. He described it as a "hassle free experience." He suggested that it is a viable way to deliver medicine to children in the United States.

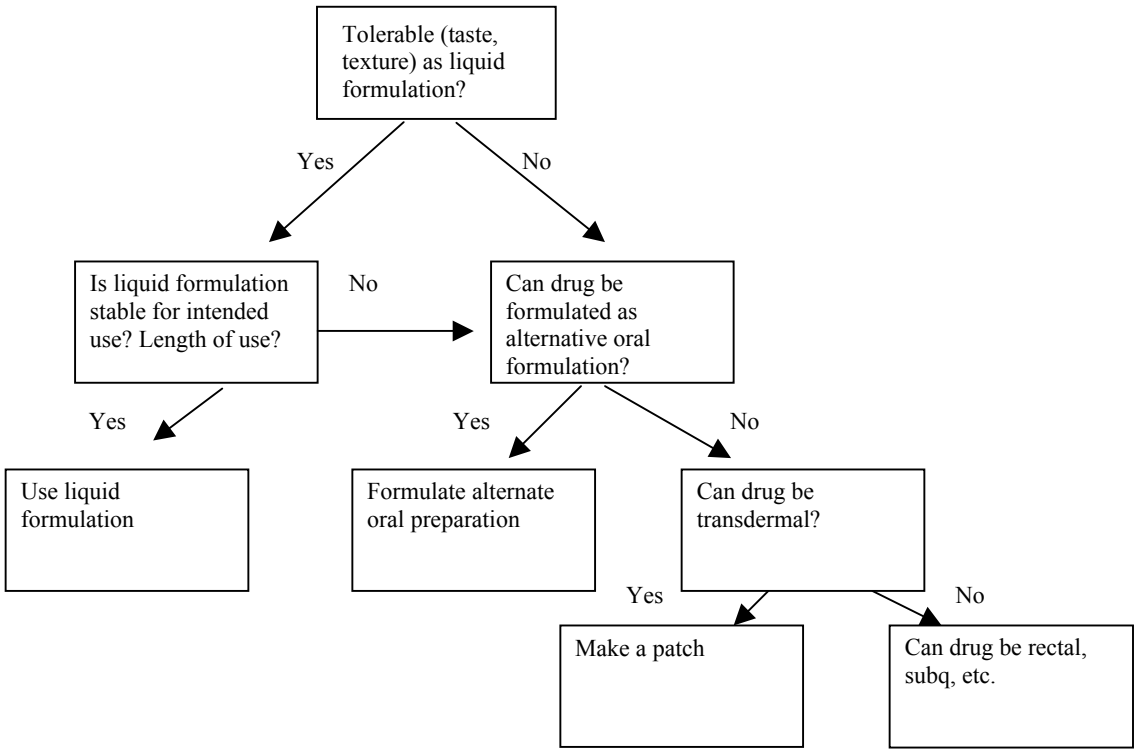
Dr. Walson mentioned a few scientific issues, including irritation, absorption, and chronic use. He said that in a hospital he worked in, rectal administration of medicine required a same sex administrator, regardless of the age of the child. Dr. Nunn said that practices changed in the United Kingdom after some child abuse cases. He also raised the issue of medications that require administration during school hours and he mentioned that suppositories are fixed dose medications. He said that uniformity of drug within a suppository would be necessary before pharmacists could manipulate the dose.

New Technologies and Drug Delivery Systems
Chair: H. William Kelly, Pharm.D.
Facilitator: William Rodriguez, M.D., Ph.D.

Dr. Kelly said that his group decided to discuss how new technologies interfaced with many of the issues that had been brought up, including economics. As an example, they asked why a specific new technology—a drinking straw that delivered clarithromycin—was commercially developed. The answer is that there is a large need for an oral antibiotic for young children. This drinking straw technology is not particularly stable and it has a horrible taste, so it includes a taste masking technology. The pharmaceutical industry spent a lot of money developing it because it was economically feasible. The question the group pondered is how new technologies for formulations that are not as economically promising can be developed.

The action items for new technologies for delivery systems should be considered after the drug list is prioritized. The action items include:

- Assemble the information that currently exists on available extemporaneous formulations
- Determine that there are appropriate indications in the pediatric population (Dr. Walson's "me too" drug)
- Know the physical, chemical, pharmacokinetic, and biopharmacological properties of the drug
- Available compounding frequency information
- Determine whether a new formulation/technology is appropriate
- Prepare a decision tree (example is below).



Questions and Comments. Dr. Kauffman said the group also discussed picking one or two key compounds and piloting this approach to see how it works. Another participant commented that prioritizing new drug delivery systems had not been previously discussed and would depend on analysis of the list of formulations needed and the delivery systems available for each.

A Dialogue with the EMEA Formulation Group and NICHD's PFI

Moderators: Tony Nunn, Ph.D., and George Giacoia, M.D.

Dr. Giacoia and Dr. Nunn led a discussion on the possible value of having a transatlantic collaboration concerning some of the issues discussed during the PFI meeting. Dr. Nunn said that much of what had been discussed here has also been discussed in Europe. Collaboration might reduce costs, make the regulatory process easier, and open up larger markets for products. He said that the British Pharmacopoeia is writing monographs that are very similar to those being produced by the USP. Collaboration could prevent duplication of effort.

Dr. Giacoia said that Table 3 in the report prepared by Dr. Nunn relates age to the type of formulation and is fundamental to this initiative. This is another area for possible collaboration. Dr. Nunn said that if the initiative takes a global view and considers anti-malarials and anti-retrovirals, one needs solid dosage forms, not liquids, for African children. In his opinion, very little science supports current opinions on which formulations are most appropriate for children.

One participant remarked that in some cases, African children had been taught to swallow adult dosage forms (larger tablets). Dr. Nunn said that a couple of papers published in educational psychology journals had described that process.

Dr. Giacoia asked Dr. Nunn if PUMA might provide funding for pediatric formulation development. Dr. Nunn said that reducing costs or incentivizing industry can help formulation development and that much discussion has occurred on how to reward developing pediatric formulations for off-patent drugs. The European Better Medicines for Children regulations contain a clause called Pediatric Use Marketing Authorization (PUMA), which gives 10 years of data protection to a company that develops a pediatric formulation for an off-patent drug. In the case of orphan drugs, that protection is extended to 12 years. Discussions on the potential benefits of having similar incentives and pathways on both sides of the Atlantic have been taking place.

Dr. Nunn was asked how data protection provides companies with an economic advantage. He responded that he was not yet totally familiar with this new legislation, but his understanding is that if a company develops a formulation and takes it to the marketplace, the data will be protected by competitors. Dr. Van Den Anker added that the pediatric board that will be created can prevent other companies from making similar formulations. The regulations are not yet approved, but Dr. Nunn and Dr. Van Den Anker expect them to take effect in 2007.

Dr. Walson said there was a possibility that the off-patent product would be able to use the innovator's brand name, which would be an incentive for the innovator to create the pediatric

formulation itself. Dr. Nunn said that he thought the regulations allow the innovator to use their brand name when they develop a pediatric formulation. He also believes that the brand safety and efficacy data can be used as part of the application. However, he said it would be best if he reviews and then provides more information on this aspect of the regulations.

Dr. Nunn said one of the reasons he came to the PFI meeting was to explore ways to avoid duplication of effort. One way is to see which drugs and monographs on the priority list are already marketed in appropriate formulations in other countries. In addition, overlap exists globally on the need for certain pediatric formulations, and it would make sense to divide that work, which perhaps could be done through the pharmacopeias. Dr. Nunn said that his paper "Formulations of Choice for Pediatric Populations," which was distributed before the meeting, tried to clarify the state of pediatric formulations in Europe. He hopes that if this group plans on writing similar position papers, it builds on what has already been done in Europe. He said that although Europe has determined where it is in the formulation development process, it lacks an infrastructure similar to what has been developed in the United States. He will take back some of the ideas generated during this meeting to his colleagues in Europe.

In summary, issues common to both Europe and the United States are:
- Scientific issues
- Funding issues
- Prioritization of drugs in need of pediatric formulation
- Interactions between EMEA formulation group and PFI groups
- Global market issues
- Cultural differences.

United Kingdom and United States Formulation Lists

	United Kingdom	**United States**	
Preparations in list	42	108	
Authorized/labeled in UK, EU, Australia		28	26%
Common to both lists	24	24	22%
UK also interested		43	40%
Subtotal		95	88%
UK not currently interested		17	16%

A participant said that he did not think the intent of the BPCA was to provide drugs to children after they have been available for adults for10 years. Dr. Nunn replied that once the new regulations are in place in Europe, a pediatric formulation plan is required in order to have an adult formulation authorized. He added that the FDA may need to be pushed to find out why medicines that are authorized for children in appropriate formulations in Canada, Europe, and

Australia, are not allowed to be imported for American children. From a risk management perspective, these formulations would be much safer than on-the-bench compounding.

Dr. Nunn and Dr. Giacoia then discussed extemporaneous preparations in the United States and Europe. The European system has extemporaneous compounding but they also have "halfway houses," which manufacture to GNP standards. This provides quality assurance, but not safety or efficacy. The regulatory body audits facilities that produce to GNP standards. Other issues discussed included:

- Regulatory issues in accepting formulations licensed by EMEA or individual member states (or labeled by the FDA)
- Definition of pediatric formulations for developmental age (studies needed)
- Guideline (for example, ICH) on pediatric formulations (is one required?)
- Comparison of incentives (and/or proposed incentives in Europe and the United States)
- Comparison between EMEA and U.S. incentives for orphan drugs
- Role of generics in developing pediatric formulations (and "specials" companies in the United Kingdom).

Regarding performance of studies of pediatric formulations, the following topics were discussed:

- Development of an integrated program to develop needed pediatric formulations on off-patent drugs
  - Role of industry
  - "Specials" and compounding laboratory roles
  - Role of individual hospitals (standards)
  - Role of regulators
- Bioavailability research studies
- PK/PD/safety studies in European and U.S. networks
- Liaison with industry when developing new pediatric formulations.

Dr. Nunn said that the economics of a generics company taking on development of pediatric formulations has been discussed several times during the meeting. In the United Kingdom, there are intermediate companies called "specials" that are authorized by the regulatory authority, and a number of them specialize in liquid medicines for children and the elderly. He thinks this is a niche that can be tapped. Other roles of pharmaceutical companies include:

- Role of generics in developing pediatric formulations
- Willingness of sponsors to apply for U.S. patents for formulations licensed by EMEA and vice versa
- Willingness of sponsors to develop pediatric formulations that would be simultaneously labeled in Europe and the United States
- What are the barriers to provision of information on
  - Formulation (recipe)
  - Primary physicochemical data
  - Problems for children with adult dosage form
  - Critical functional components
  - Dosage uniformity
  - Testing

- What are the barriers to provision of active substances?

Dr. Nunn said that a liquid formulation is often produced for phase 1 studies, but other formulations (tablets) may be used for phase 2 and 3 studies. What is done with the information on formulating the liquid that may be useful to compounding? European regulators are working with pharmaceutical industry representatives to examine legal barriers to obtaining this information. They are also discussing transfer of property and intellectual property rights for formulations that are not marketed or are discontinued. He said that captopril is manufactured by Bristol-Myers Squibb (BMS) in Australia and has been imported into Europe for many years. Last year, BMS decided to discontinue production, and the British Pharmacopoeia Commission was negotiating to allow intellectual property rights to that formulation to be made public. BMS decided not to discontinue production. Dr. Nunn pointed out that this formulation has never been imported into the United States. He added that active ingredients are often purchased from China, India, and Russia and the quality of those products can be a concern. He asked why the U.S. pharmaceutical industry cannot sell quality assured active substances for safer compounding.

Dr. Walson wondered if products are kept away so that more expensive alternative products are used. He asked whether, if intellectual property is moved into the public domain in the United Kingdom, it is then available to the rest of the world. Dr. Nunn said that the effort was to collaborate, not to force companies to release proprietary information. A member of the scientific working group suggested shifting legal liability to the public domain with the intellectual property. Right now, it is very hard for compounding pharmacists to obtain this type of information.

The final set of issues concerned extemporaneous formulations. Topics discussed included:
- Scope of use extemporaneous preparations in Europe and the United States
- Quality control/assurance issues
- Harmonization of extemporaneous formulations between Europe and the United States (Canada, Japan, Australasia)
- Common formularies
  - United States
  - Europe
  - World Health Organization (looking at its essential drugs list).

Future Steps

Donald Mattison, M.D.

Dr. Mattison thanked everyone for participating in this planning meeting. The intent is to:
- Summarize the discussions
- Make the summaries available on the Web site
- Publish thoughts and suggestions from the working groups
- Evaluate short- and long-term objectives
- Create an infrastructure to help reach those objectives
- Respond to questions raised.

Some of the mechanisms for future steps include making announcements to indicate interest in research proposals, generating contracts to generate information to enhance pediatric formulations, and developing initiatives in line with NIH technology development activities.

There is a strong push within the NIH to improve translation of science generated from NIH funding, and the PFI fits within that roadmap. Future activities include:

- Maintaining contact with participants
- Working with group chairs to plan future conference calls
- Working on information gathered
- Identifying ways to help companies develop pediatric formulations
- Facilitating academic research.

Dr. Mattison thanked everyone for helping to enhance the safety of pediatric therapeutics.

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